[2,4-DICHLOROPHENOXYACETIC ACID] Developmental Toxicity Study - Rat [§83-3(a)/OPPTS 870.3700]

Supplement to DER for ACCESSION NO. ~~00251031~~ - Developmental Toxicity Study - Rat [2,4-Dichlorophenoxyacetic Acid] MRID 00130407

This supplement provides an EXECUTIVE SUMMARY and data tables to upgrade the re-review [Document Nos. 011934] of the original DER [Document No. 003887].

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AMENDED DATA EVALUATION RECORD

STUDY TYPE: developmental toxicity - rat § 83-3(a)/OPPTS 870.3700
DP BARCODE: N/A SUBMISSION NO.:
P.C. CODE: 030001
CASWELL NO.:315 CAS NO.: 94-75-7
TEST MATERIAL (PURITY) : 2,4-Dichlorophenoxyacetic acid [%]
SYNONYMS: 2,4-D
SPONSOR: Industry Task Force on 2,4-D Research Data

CITATION: Nemec, M. D.; Tasker, E. J.; Werchowski, K. M.; *et al.*. (1983). A Teratology Study in Fischer 344 Rats With 2,4-Dicholorphenoxyacetic Acid. WIL Research Laboratories, Inc.; Study No. WIL-81135. Accession No. 00251031. Document No. 011934. Unpublished. MRID 00130407

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EXECUTIVE SUMMARY: In a developmental toxicity study [Accession No. 00251031], pregnant Fischer 344 rats [35/group] were administered 2,4-dichlorophenoxyacetic acid [97.5%] *via* gavage at dose levels of 0 [corn oil], 8 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day from gestation day [GD] 6 through gestation day 15.

There were no treatment-related deaths. Two [one control and one low-dose] dams delivered prematurely on gestation day 19, and in both instances the offspring produced were of similar size and development as those from full-term delivery. Clinical signs were comparable among the groups. Body weights were comparable among the groups throughout the study, but dams at the high-dose level displayed a decrease in body-weight gain during the dosing period [79% of control for GD 6-15; 57% of control for GD 6-10], although statistical significance was not attained. The corrected body-weight gain was comparable among the groups. Food consumption data were not reported.

The was a slight decrease in pregnancy rate with increasing dose [85%, 85%, 80% and 77%]. The numbers of corpora lutea, implantations, and live fetuses were comparable among the groups, and there were no dead fetuses. The number of resorptions, as well as pre- and post-implantation losses, were not adversely affected by treatment. The number of the dams with 100% resorptions was 2, 0, 1, and 1 [control, low-, mid-, and high-dose groups,

respectively]. One control, 2 low-, 4 mid-, and 2 high-dose dams had late resorptions. Fetal body weight and crown-rump length were comparable among the groups, as was the sex ratio.

There were no statistically-significant or treatment-related differences in the incidence of fetal external or visceral malformations. There was an increased incidence of skeletal malformations/variations at the high-dose level that included the presence of 7th cervical ribs [4 fetuses in 3 litters *vs* none in the control], presence of 14th rudimentary ribs [4 fetuses in 3 litters *vs* none in the control]; malaligned sternebrae [15 fetuses in 10 litters *vs* 7 fetuses in 7 litters of the control]; reduced ossification of the vertebral arches [6 fetuses in 5 litters *vs*2 fetuses in 1 litter of the control]; and unossified sternebrae # 5 or #6 [73 fetuses in 22 litters (3.32 fetuses/litter) *vs* 62 fetuses in 24 litters (2.58 fetuses/litter)]. Although none of the increases attained statistical significance, they were attributed to treatment since some of the findings [maligned sternebrae, 14th rudimentary ribs, and reduced ossification of vertebral arches] were also observed in the F1b pups of dams fed 2,4-D at 80 mg/kg/day [actual dose ≈75 mg/kg/day] in the 2-generation reproduction study in the same strain of rat. Additionally, skeletal findings [2nd wavy *ribs, lumbar ribs*] and missing sternebrae were observed in another developmental toxicity study using a different strain of rat [Sprague-Dawley] at a comparable dose of 87.5 mg/kg/day [2,4-D].

The maternal toxicity NOAEL is 25 mg/kg/day, and the maternal toxicity LOAEL is 75 mg/kg/day, based on decreased body-weight gain.

The NOAEL for developmental toxicity is 25 mg/kg/day, and the developmental toxicity LOAEL is 75 mg/kg/day, based on increased incidence of skeletal abnormalities.

This developmental toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3700; §83-3(a)] for a developmental toxicity study in the rodent. NOTE: In 1996, it was determined that the original DER [Document No. 003887] was inadequate, and the study was re-evaluated [Document No. 011934]. The NOEL/LOEL were the same in both reviews. The current EXECUTIVE SUMMARY does not alter the no-effect and effect levels but reflects current terminology for the no-observed-adverse-effect level [NOAEL] and lowest-observed-adverse-effect level [LOAEL]. Additionally, the presence of 7th cervical ribs and 14th rudimentary ribs are considered skeletal malformations; previously listed as skeletal variations.

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Table 1. Maternal Body Weight/Gravid Uterine Weight/Corrected Body Weight/Gain [grams]				
Dose✦/Day	0 mg/kg/day	8 mg/kg/day	25 mg/kg/day	75 mg/kg/day
body weight				
0	198±11	196±12	193±10	201±13
6	207±14	208±15	203±12	210±13
10	214±16	213±15	210±12	214±13
12	219±18	217±16	214±12	218±13
15	225±13	226±17	223±13	226±15
20	261±22	262±26	260±20	262±25
body-weight gain				
0-6	9±5	11±5	9±8	9±4
6-10	7±5	5±4	7±6	4±4 [57]√
10-12	5±6	5±3	4±3	4±2
12-15	7±14	8±4	9±3	7±4
15-20	34±14	36±12	37±12	37±14
6-15	19±8	18±6	20±8	15±7 [79]
0-20	62±21	66±17	67±17	61±19
gravid uterine weight	42.1±17.9	45.5±16.4	44.5±13.5	42.6±16.1
corrected body weight	217.1±12.8	217.1±15.6	214.9±12.5	219.5±14.9
corrected BWG [0-20]	18.3±7.9	20.7±6.3	21.5±7.6	18.5±6.9

√[% of control]; data from Tables 9-11, pages 32-52 of the report

Table 2. Resorptions				
Parameter/dose	0 mg/kg/day	8 mg/kg/day	25 mg/kg/day	75 mg/kg/day
# dams w/ resorptions				
early	9	8	8	8
late	1	2	4	2
# dams w/out viable fetuses	2	0	1	1